Medicaid Executive Summary for Immediate-Release (IR) *Requip* for Parkinson's Disease

- IR *Requip* is a selective non-ergoline dopamine D_2/D_3 agonist indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease (PD).[1]

BACKGROUND:

- Long-term treatment of PD with L-dopa can be associated with the development of severe and sometimes debilitating adverse events that may limit its usefulness, including motor fluctuations and dyskinesias.[2,3] [4]
- Delaying the initiation of and/or decreasing the total exposure to L-dopa, may reduce the risk of motor fluctuations and dyskinesias. Early use of dopamine agonists has been suggested because as monotherapy they provide symptomatic relief and a low risk of dyskinesias in PD patients compared to L-dopa. [5] [6]
- The 2001 Treatment Guidelines for Parkinson's Disease recommend dopamine agonists as 1st line initial monotherapy for newly diagnosed PD patients, as well as adjunctive therapy to L-dopa for appropriate PD patients. [7] In addition, the 2006 AAN practice parameters support the use of dopamine agonists as initial monotherapy in treating PD symptoms and lessening motor complications. [8]

EFFICACY:

IR *Requip* use in PD as initial monotherapy:

Can significantly reduce the risk of dyskinesia vs. L-dopa.

- A 5-year study in early PD patients found significantly fewer patients treated with IR *Requip* (n =177) experienced dyskinesia compared with those treated with L-dopa (n =88) (20% vs. 45%). [9] The incidence of dyskinesia in patients on monotherapy with IR *Requip* (before L-dopa supplementation) was 5% compared to 36% of patients on L-dopa. A naturalistic extension of the 5-year study indicated initial monotherapy treatment with IR *Requip* was associated with a reduced incidence of dyskinesias for up to 10 years vs. L-dopa.[10]
- The risk of developing dyskinesia in patients receiving IR *Requip* (with or without L-dopa supplementation) was nearly three times less than that for patients receiving L-dopa. [9] Mildly disabling or worsened dyskinesia was reported in significantly fewer patients receiving IR *Requip* as compared to L-dopa (8% vs. 23%).

Provides symptom control in activities of daily living (ADLs) comparable to L-dopa.

- Monotherapy with IR *Requip* maintained ADLs comparable to L-dopa for 5 years. [9]
- At 5 years, the mean dose in patients receiving IR *Requip*, was 16.5 ± 6.6 mg/day and 34% required no supplemental L-dopa; the incidence of treatment-emergent adverse events was similar between groups (97%, IR *Requip* and 96%, L-dopa). [9]

IR *Requip* use in PD as adjunctive therapy:

Spares L-dopa dose and reduces incidence of L-dopa associated motor fluctuations ("off" time).

- In a 6-month, placebo-controlled trial in patients with advanced disease receiving concomitant L-dopa, a significantly greater percentage of patients treated with IR *Requip* (n =95) were able to achieve a 20% reduction in L-dopa dose and a 20% reduction in awake time spent "off" compared with placebo (n =54) (35% vs. 13%). [11] The mean daily dose at study endpoint was 19.1 mg ± 6 mg in patients receiving IR *Requip*. L-dopa dose was reduced 31% (242 mg/day) in patients receiving IR *Requip* vs. 6% for placebo patients (51 mg/day).

Improves Clinical Global Impressions (CGI) scores .

- In a 6-month placebo-controlled trial, CGI Improvement scores improved in 58.5% of patients receiving IR *Requip* vs. 32% with placebo. [11]

DOSING:

- IR *Requip* is a progressive therapy for a progressive disease: IR *Requip* can be titrated for treating PD from 0.75 mg/day up to a maximum of 24 mg/day to meet changing patient needs. IR *Requip* has been shown to provide efficacy across the full dosing range.
- In pooled clinical trials with IR *Requip*, 75% of responders achieved an initial response at doses up to 9 mg/day. [12]
- IR *Requip* tablets are color-coded to clearly identify dosage strength and the tablets are pentagon-shaped with beveled edges for ease of handling, an advantage to PD patients whose tremor may make it hard to handle medication.

SAFETY:

- At 5 years, the incidence of treatment-emergent adverse events was similar between groups (97%, IR *Requip* and 96%, L-dopa). [9] The most common adverse events in patients receiving IR *Requip* compared with L-dopa were nausea (49% vs. 49%), somnolence (27% vs. 19%) and insomnia (25% vs. 24%). Although there was a higher incidence of hallucinations with IR *Requip* (17%) compared to L-dopa (6%), they were mild and easily managed in most patients; leading to withdrawal in 4% and 2% of patients, respectively.
- **IR *Requip* has been associated with sedating effects, including somnolence, and the possibility of falling asleep while engaged in activities of daily living, including operation of a motor vehicle.** IR *Requip* should be discontinued if these events occur; it is unknown if dose reduction will eliminate episodes of somnolence. Prescribers should reassess patients for somnolence throughout treatment.
- Syncope or symptomatic hypotension may occur, particularly during initial treatment or dose titration. Patients should be cautioned against rising rapidly after sitting or lying down. Because of possible additive effects, caution should be exercised with patients who have sleep disorders or are taking sedating medications, alcohol, CNS depressants, or medications that increase ropinirole plasma levels.
- Patients and caregivers should be informed that impulse control symptoms, including compulsive behaviors such as pathological gambling and hypersexuality, have been reported in patients treated with dopaminergic agents, including IR *Requip*. These behaviors were reported principally in PD patients treated with dopaminergic agents, especially at higher doses.
- Hallucinations may occur at any time during treatment. IR *Requip* may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate pre-existing dyskinesias.

REFERENCE(S)

1. Prescribing Information. Requip®. *
2. Ahlskog JE and Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Movement Disorders 2001;16(3):448-58.*
3. Poewe WH and Wenning GK. The natural history of Parkinson's disease. Neurology 1996;47(6 Suppl 3):S146-52.*
4. Schrag A and Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain 2000;123(Pt 11):2297-305.*
5. Watts RL. The role of dopamine agonists in early Parkinson's disease. Neurology 1997;49 (Suppl 1):S34-S48.*
6. Rascol O and Fabre N. Dyskinesia: L-dopa-induced and tardive dyskinesia. Clin Neuropharmacol 2001;24(6):313-23.*
7. Olanow CW, Watts RL and Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 2001;56(Suppl 5):S1-S88.*
8. Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review. Report of the quality standards subcommittee of the American Academy of Neurology. Neurology 2002;58:11-17.*
9. Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 2000;342:1484-91.*
10. Hauser RA, Rascol O, Korczyn AD, et al. Ten-year follow-up of Parkinson's Disease patients randomized to initial therapy with ropinirole or levodopa. Mov Disord 2007;22(16):2409-2417. SKF-101468/170.*
11. Lieberman A, Olanow CW, Sethi K, et al. A multicentre trial of ropinirole as adjunct treatment for Parkinson's disease. Neurology 1998;51:1057-1062.*
12. Korczyn AD, Thalamas C and Adler CH. Dosing with ropinirole in a clinical setting. Acta Neurol Scand 2004;106:200-2004.*